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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,871	09/16/2005	Andreas Kunkel	7003/55	2451

27774 7590 11/14/2007  
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EXAMINER
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MEAH, MOHAMMAD Y

ART UNIT	PAPER NUMBER
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1652

MAIL DATE	DELIVERY MODE
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11/14/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/549,871

Applicant(s)

KUNKEL ET AL.

Examiner

Mohammad Meah

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 13 August 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-32 is/are pending in the application.
- 4a) Of the above claim(s) 11-14, 19-22, 25- 28 and 30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 1-2, 4-5, 9, 15, 17, 24, 29 and 31-32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

Claims 1-32 are pending. Claims 1-10, 15-18, 23-24 and 29 were examined in the previous action. Claims 11-14, 19-22, 25- 28 and 30 remain withdrawn. With supplemental amendment of this application, the applicant, on dates on 8/13/07, amended claims 1-2, 4-5, 9, 15, 17, 24, 29 and added new claims 31-32

### ***Claim Rejections***

Applicants' arguments filed on 8/13/07, have been fully considered and are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections not reiterated from previous office actions are hereby withdrawn.

#### ***USC 112 rejection 2<sup>nd</sup> paragraph***

Rejection of claims 1-10, 15-18, 23-24 and 29 under USC 112 rejection 2<sup>nd</sup> paragraph is withdrawn after applicants amendment of the claims.

### ***35 U.S.C 112 1ST paragraph Rejections***

#### ***Written Description requirement Rejections:***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 15-18, 23-24, 29, 31-32 are rejected under 35 U.S.C. 112, first

paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-10, 15-18, 23-24, 29, 31-32 are directed to a process of producing ergosta-5,7 dienol and many prenyl compounds by culturing organisms having a decreased desaturase activity wherein desaturase gene inactivated by any mutagenesis, an increased HMG-CoA reductase activity and overexpression of the squalene epoxidase of SEQ ID NO:8 or a variant thereof from any source. The specification fails to describe in any fashion the physical and/or chemical properties of the claimed class of biosynthetic intermediates and /or metabolites thereof or class of ergosterol-biosynthetic enzymes including squalene epoxidase other than its involvement in ergosterol biosynthetic pathway. No relation between the structure of the species and function is described. Neither the structure of the compounds produced in the method of using organisms nor the structure of genes expressed in the organism are defined in the specification. The specification discloses only a few DNA of the claimed genus of desaturase, HMG-CoA reductase and squalene epoxidase (i.e., SEQ ID Nos : 2, 4, 8 ) expressed in the microorganism for the production of few ergosterol compounds ( i.e., lanosterol, Zymosterol, 4,4 dimethyl-zymosterol), which are insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

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Applicants argue that the claims require for their methods of production of 7-dehydrocholesterol/ other cholesterol products, organisms having increased expression of any squalene epoxidase and HMG-CoA reductase of SEQ ID NO: 4 and reduced activity of desaturase by desaturase gene inactivated by any mutagenesis the specification discloses several of these enzymes(squalene epoxidase of SEQ ID NO: 8 and HMG-CoA of SEQ ID NO: 4 . However, this is not persuasive because the scope of variant of squalene epoxidase of SEQ ID NO: 8 and HMG-CoA reductase and of desaturase encompassed is undefined. Preparation of most of them require controlled involvement of multiple IPP biosynthetic pathway enzymes. However prenyl compounds recited in the instant claims comprise variety of compounds comprising any structure. The specification fails to describe how a genus of prenyl compounds which comprise any number of isoprenoid unit can be produced from a genus of transformed microorganism comprising increased expression squalene epoxidase and HMG-CoA reductase and decreased expression of any desaturase by any means . There are many way expression of squalene epoxidase and HMG-CoA reductase be increased and desaturase be decreased in an organism. As the structure of the claimed all squalene epoxidases and HMG-CoA reductases and desaturases that recite in the instant claims as well as the structure of the claimed prenyl alcohol are not defined in any way, one of ordinary skill in the art would not be able to make any such compound using any microorganism comprising said enzymes and require would undue experimentation to first find what specific prenyl compound in fact fall within the claimed class of prenyl compounds are the product of any mutant microorganisms comprising increased expression of squalene epoxidase and HMG-CoA reductase and decreased

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expression of desaturase. Moreover, there are many ways in which a microorganisms' desaturase genes can be inactivated such as deletion, substitution of specific amino acid residues of DNA sequence or deletion of the whole genes, etc. Also disclosed species of squalene epoxidase and HMG-CoA reductase (SEQ ID NO:8 and SEQ ID NO: ) are not representative of any variant of SEQ ID NO:8 and SEQ ID NO: 4. It is well known in the art that variants of a gene can alter both the structure and function of the protein encoded thereby in many different ways. As such the disclosed species are not representative of the structure and function of all members of the genus claimed

Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

***Enablement Rejections:***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 15-18, 23-24, 29, 31-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of producing ergosta-5,7 dienol or few ergosterol compounds ( i.e., lanosterol, Zymosterol, 4,4

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dimethyl-zymosterol) by culturing mutant *S. cerevisiae* *Erg5* having deleted 22-desaturase gene and overexpressing said strain with HMG-CoA reductase gene comprising SEQ ID NO: 3 and squalene epoxidase gene of SEQ ID NO:7, does not reasonably provide enablement for process of producing prenyl compound by culturing any organisms having decreased desaturase activity and increase of any HMG-CoA reductase activity which overexpress any squalene epoxidase or squalene epoxidase having 30% sequence identity to SEQ ID NO:8 and any HMG-CoA reductase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and for use the invention commensurate in scope with these claims.

Claims 1-10, 15-18, 23-24 and 29 are so broad as to encompass any process of producing any prenyl compound by culturing organisms having decreased desaturase activity and increase of any HMG-CoA reductase activity which overexpress any squalene epoxidase or squalene epoxidase having 30% sequence identity to SEQ ID NO:8 and any HMG-CoA reductase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number processes of producing prenyl compound by culturing organisms having decreased desaturase activity and increase of any HMG-CoA reductase activity which overexpress any squalene epoxidase or squalene epoxidase having 30% sequence identity to SEQ ID NO:8 broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the

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desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a process of producing ergosta-5,7 dienol by culturing organisms having decreased desaturase activity of a few desaturases and increase of a few HMG-CoA reductases and overexpression of squalene epoxidase ( SEQ ID Nos:2, 4, 8, 10, 12, etc).

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable (e.g., Whisstock, et al. Quarterly Rev. Biophy. 2003, 36, pp 307-340). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any process of producing prenyl compound by culturing organisms having decreased desaturase activity by desaturase gene inactivated by any mutagenesis and increase of any HMG-CoA reductase activity and overexpression of any squalene epoxidase or squalene epoxidase having 30% sequence identity to SEQ ID NO:8

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because the specification does not establish: (A) regions of the protein structure which may be modified without effecting desaturase, HMG-CoA reductase and squalene epoxidase activity; (B) the general tolerance of desaturase, HMG-CoA reductase and squalene epoxidase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any desaturase, HMG-CoA reductase squalene or epoxidase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any process of producing prenyl compound by culturing organisms which desaturase activity is decreased by any means and increase of any HMG-CoA reductase activity which overexpress any squalene epoxidase or squalene epoxidase having 30% sequence identity to SEQ ID NO:8 polypeptide with an enormous number of modifications of amino acid residues of a protein having amino acid sequence of SEQ ID NO: 8. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of squalene epoxidase, having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants contend that claims 1-10, 15-18, 23-24 and 29 , 31-32 meet the enablement requirement of § 112, first paragraph specification explains how farnesol is produced by using recombinant organism expressed with a full-length HMG-CoA-reductase gene encoding SEQ ID NO: 4 or squalene epoxidase of SEQ ID NO: 8. However, this is not persuasive as the scope of variant of genes encompassed in the instant claims are undefined . and undefined also the prenyl compound made that recited in the instant claims. There are many way expression of squalene epoxidase and HMG-CoA reductase be increased and desaturase be decreased in an organism. As the structure of the claimed all squalene epoxidases and HMG-CoA reductases and desaturases that recite in the instant claims as well as the structure of the claimed prenyl compound are not defined in any way, one of ordinary skill in the art would not be able to make any such compound using any microorganism comprising said enzymes and require undue experimentation to first find what specific prenyl compound in fact fall within the claimed class of prenyl compounds and are the product of any mutant microorganisms comprising increased expression of squalene epoxidase and HMG-CoA reductase and decreased expression of desaturase. Moreover, there are many ways in which a microorganisms' desaturase genes can be inactivated such as deletion, substitution of specific amino acid residues of DNA sequence or deletion of the whole genes, etc. Also disclosed species of squalene epoxidase and HMG-CoA reductase (SEQ ID NO:8 and SEQ ID NO: ) are not representative of any variant of SEQ ID NO:8 and SEQ ID NO: 4. As such the disclosed species are not sufficient guidance to make and use any variant of SEQ ID NO:4 or 8. It is well known in the art that variation of a gene by mutation, substitution of nucleotide

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residues can alter both the structure and function of the protein encoded thereby in many different ways. As such the disclosed species are not sufficient to predict the effects of any mutation on the structure and function of all members of the genus claimed.

***CLAIM Rejection - 35 U.S.C 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejection of Claims 1-8, 15-16, 23-24 and 29 under 35 U.S.C. 102(b) as being anticipated by Saunders et al. ( EP 0486290 –IDS reference is withdrawn after applicants amendment of claims and arguments.

Rejection of 1-8, 15-16, 23-24 and 29 under 35 U.S.C. 102(b) as being anticipated by Weber et al. (WO-99/16886–IDS reference is withdrawn after applicants amendment of claims and arguments.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu

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Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-

9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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